What is claimed is:

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- 1. A composition comprising a hydrophilic portion and a hydrophobic 1 portion joined by an ortho ester linker, wherein the ortho ester linker hydrolyzes at an 2 increasing rate as the pH is reduced below 7. 3
- 2. The composition of claim 1, wherein the hydrophilic portion comprises a 1 polymer capable of increasing circulation time in the bloodstream of animals when 2 3 incorporated on the surface of an encapsulator.
 - 3. The composition of claim 2, wherein the hydrophilic portion comprises methoxypolyethylene glycol.
 - 4. The composition of claim 2, wherein the hydrophilic portion is selected from the group consisting of polyethyleneglycol, hydroxylated dendrons, poly(methyloxazoline), poly(ethyloxazoline) and polyvinylpyrrolidone.
 - 5. The composition of claim 2, wherein the hydrophilic portion comprises polyethyleneglycol having a molecular weight from 200 to 20000.
 - The composition of claim 1, wherein the hydrophilic portion comprises a 6. targeting ligand.
 - 7. The composition of claim 1, wherein the hydrophilic portion comprises a cationic group.
 - 8. The composition of claim 7, wherein the cationic group is selected from the group consisting of primary amines, secondary amines, tertiary amines, quaternary ammoniums or imidazoles.
- 9. The composition of claim 1, wherein the hydrophobic portion is selected from the group consisting of diacyl glycerols, distearoylglycerol, dipalmitoylglycerol, 2 3 dimyristoyl glycerol, dioleoyl glycerol.
 - 10. The composition of claim 1, wherein the hydrophobic portion is selected from the group consisting of tocopherol, cholesterol, coenzyme Q, and ceramide.

- 12. The composition of claim 11, wherein the ortho ester linker comprises a 1 diketene acetal derivative. 2
- 13. The composition of claim 11, wherein the ortho ester linker comprises a 1 2 3,9-dialkoxylated 3,9-Diethyl-2,4,8,10-tetraoxaspiro[5,5]undecane derivative.
- 14. The composition of claim 11, wherein the composition comprises 3,9-1 2 Diethyl-3-(2,3-distearoyloxypropyloxy)-9-(methoxypolyethyleneglycol2000-1-yl)-2,4,8,10-tetraoxaspiro[5,5]undecane. 3
 - 15. The composition of claim 1, wherein the ortho ester linker comprises a single ortho ester.
 - 16. The composition of claim 15, wherein the ortho ester linker comprises a dichloromethylmethyl ether derivative and the hydrophilic portion is cationic.
 - 17. The composition of claim 16, wherein the composition comprises N,Ndimethyl-(4-methoxy-(cholest-5-en-3 β -oxy)hept-3,5-dioxa-yl)ammonium (DOC).
 - 18. The composition of claim 16, wherein the composition comprises N, N, N-trimethyl-(4-methoxy-(cholest-5-en-3 β -oxy)hept-3,5-dioxa-yl)amine iodide.
- 19. A composition comprising an encapsulator, wherein the encapsulator 1 comprises the composition of claim 1. 2
- 20. The composition of claim 19, wherein the encapsulator further 1 2 comprises a lipid.
- 21. The composition of claim 20, wherein the lipid comprises DOPE. 1
- 22. The composition of claim 21, comprising DOPE/POD in a ratio of about 1 97:3 to 85:15. 2

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- 23. The composition of claim 21, comprising DOPE/DOC.
- 1 24. The composition of claim 20, wherein the lipid comprises a fusogenic 2 lipid.
- 1 25. The composition of claim 20, wherein the lipid comprises a lipid selected 2 form the group consisting of phosphatidylcholine, phosphatidylglycerol,
- 3 phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, cholesteryl
- 4 hemisuccinate, cholesterol sulfate, ceramide, cardiolipid, N[1-,2dioleoyl-3-
- 5 trimethyl]ammonium propane (DOTAP), dimethyldioctadecylammonium bromide
- 6 (DDAB), 1-palmitoyl-2-oleoyl-sn-glycero-3-ethyl-phosphocholine,N[1-(2,3-
- odioleyloxy)propyl]-N,N,N,-triethylammonium (DOTMA),triglycerides, squalene, coenzyme Q and alkyl acylcarnitine esters.
 - 26. The composition of claim 20, wherein the lipid further comprises a targeting ligand.
 - 27. The composition of claim 26, wherein the targeting ligand is selected a group consisting of hyaluronan, antibodies, peptides, folate, receptor antagonists, carbohydrates, transferrin, protein hormones, and cytokines.
 - 28. The composition of claim 19, wherein the hydrophilic portion comprises a targeting ligand.
- 1 29. The composition of claim 28, wherein the targeting ligand is selected a group consisting of hyaluronan, antibodies, peptides, folate, receptor antagonists, carbohydrates, transferrin, protein hormones, and cytokines.
- 30. An encapsulator for delivering a compound, comprising an amphipathic low pH sensitive lipidic composition wherein the encapsulator exhibits degradation of less than 10% within 3 hours at a pH of 7.4 and degradation greater than 50% within 60 min at a pH of 5.0.

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- 1 32. The encapsulator of claim 31, wherein the hydrophilic portion comprises PEG.
- 1 33. The encapsulator of claim 32, wherein the ortho ester linker comprises a diketene acetal derivative.
 - 34. The encapsulator of claim 30, further comprising a lipid.
 - 35. The encapsulator of claim 30, wherein the lipid is selected from the group consisting of phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, cholesteryl hemisuccinate, cholesterol sulfate, ceramide, cardiolipid, *N*[1-,2dioleoyl-3-trimethyl]ammonium propane (DOTAP), dimethyldioctadecylammonium bromide (DDAB), 1-palmitoyl-2-oleoyl-sn-glycero-3-ethyl-phosphocholine,*N*[1-(2,3-dioleyloxy)propyl]-*N*,*N*,*N*,-triethylammonium (DOTMA), triglycerides, squalene, coenzyme Q and alkyl acylcarnitine esters, and dioleoylphosphatidyl ethanolamine (DOPE).
 - 36. The encapsulator of claim 33, wherein the hydrophilic portion comprises PEG, further comprising a lipid.
 - 37. The encapsulator of claim 30, wherein the ortho ester linker comprises a dialkoxy methoxy methine group
- 38. A method for delivering a drug to a cell comprising the steps of providing an encapsulator comprising an LOC and the drug and administering the encapsulator.
- The method of claim 38, further comprising the steps of reducing pH, degrading the encapsulator and releasing the drug. Add support active lowering of pH

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- 42. A method for incorporating an LOC into an encapsulator comprising the 1 step of mixing the encapsulator with the LOC. 2
 - 43. The method of claim 42, further comprising the steps of:
 - a) preparing a dry film of the LOC;

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- b) rehydrating the LOC to form micelles; and
- c) combining the micelles with an encapsulator suspension.
- 44. The method of claim 42, wherein the encapsulator comprises a cationic lipoplex further comprising the steps of preparing a cationic lipoplex and coating the lipoplex with the LOC.
 - 45. The method of claim 42 further comprising the steps of:
 - preparing a dry film of the LOC; a)
 - b) preparing an encapsulator suspension; and
 - c) combining the encapsulator suspension with the dry film.
 - The method of claim 42, further comprising the steps of: 46.
 - a) preparing the LOC in a non-aqueous, water miscible solvent
 - b) preparing an encapsulator suspension; and
- c) combining the encapsulator suspension with the LOC in the water miscible solvent.
- 47. The method of claim 46, wherein the non-aqueous, water miscible solvent is selected from the group consisting of acetonitrile, dimethylsulfoxide, glyme, methylpyrolidone, ethanol, triacetin and mixtures of these.
- 48. 1 A method for storing an encapsulator for delivering a compound, 2 comprising the steps of:

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- a) providing an encapsulator comprising an amphipathic low pH sensitive lipidic compound wherein the encapsulator exhibits degradation of less than 10% within 3 hours at a pH of 7.4 and degradation greater than 50% within 60 min at a pH of 5.0; and
 - b) lyophilizing the encapsulator.
- 1 49. The method of claim 48, further comprising the step of milling the 2 lyophilized encapsulator to form a dry powder.
 - 50. A method for gene transfer comprising the steps of:
 - a) providing encapsulator comprising an amphipathic low pH sensitive lipidic composition and a polynucleotide;
 - b) administering the encapsulator to an animal;
 - c) reducing the pH to degrade the encapsulator; and
 - d) releasing the polynucleotide.
 - 51. The method of claim 50, further comprising the step of forming a dry powder formulation from the encapsulator prior to administering the encapsulator.
 - 52. The method of claim 51, further comprising the step of rehydrating the encapsulator prior to administering the encapsulator.